AstraZeneca	AZD5904
Mechanism of Action	Myeloperoxidase (MPO) inhibitor http://www.ncbi.nlm.nih.gov/gene/4353
Overview	AZD5904 is a potent orally bioavailable MPO inhibitor. MPO is found in the azurophilic granules of neutrophils and in the lysosomes of monocytes and is a key enzyme involved in the oxidative production of free radicals. It produces the extremely potent oxidant hypochlorous acid (HOCl) that is a potent anti-microbial agent but can also cause tissue damage. MPO is implicated in the pathogenesis of many disorders including rheumatoid arthritis, artherosclerosis, renal glomerular injury, pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), multiple sclerosis, Alzheimer's disease, Parkinson's disease, and selected cancers. In preclinical studies, AZD5904 inhibited the isolated MPO enzyme with an IC_{50} of 140 nM and was approximately equipotent in assays of rat and mouse MPO enzyme activity. Cross over to other species has not been investigated. AZD5904 was > 10-fold selective for the related peroxide enzymes lactoperoxidase (LPO) and thyroid peroxidase (TPO) and > 70-fold selective against a panel of other targets. AZD5904 dose dependently reduced MPO activity in a rat peritonitis model with an estimated plasma IC_{50} of 5 µmol/L (~1.3 µg/mL) and elicited protective effects at comparable plasma exposures in a mouse Experimental Autoimmune Encephalomyelitis (EAE) model, although effects were not consistently reproduced. AZD5904 was in development for multiple sclerosis and COPD and has been evaluated in single and multiple dose studies in healthy volunteers.
Safety/Tolerability	A comprehensive safety assessment package has been performed on AZD5904 including pivotal reproductive toxicity studies and general toxicity studies of 6 month duration in rat and 12 month duration in dog. The thyroid and kidney were identified as target organs for toxicity; effects in thyroid may relate to activity against thyroid peroxidase. In healthy volunteers, AZD5904 has been administered as single doses of up 1200 mg and repeated doses of 32 5mg TID for up to 21 days. Studies to evaluate an extended release formulation have tested single doses up to 1400 mg and up to 600 mg BID. AZD5904 has been generally well tolerated although a minimal effect on free plasma thyroxin (T_4) and free plasma triiodothyronine (T_3) could not be ruled out in the first multiple ascending dose study.
Additional Information	Studies to date have only been conducted in healthy volunteers.
Suitable for and Exclusions	Reproductive toxicity studies support the inclusion of women of child-bearing potential in clinical studies, provided that pregnancy is prevented using a reliable form of contraception. No data are available as yet to support use in pediatrics. AZD5904 is poorly CNS penetrant. AZD5904 is renally cleared and therefore future studies will require an assessment of the risk-benefit for subjects with renal impairment, and appropriate renal function monitoring will need to be included in any trial. Proposals for use in orphan indications would be particularly welcome. Studies in multiple sclerosis, COPD, ophthalmology or dermatology are not of interest.
Clinical Trials	AZD5904 was in Phase I trials to assess safety, tolerability and pharmacokinetics following single and repeated oral doses as an extended-release formulation in healthy volunteers.
Publications	http://www.jbc.org/content/286/43/37578.full.pdf+html